[CANCER RESEARCH 51, 2885-2888, June 1, 1991]

Therapeutic Radiation at a Young Age Is Linked to Secondary Thyroid Cancer[1]

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ABSTRACT

We estimated the risk of thyroid cancer among 9170 patients who had survived 2 or more years after the diagnosis of a cancer in childhood. As compared with the general population patients had a 53-fold increased risk (9570 confidence interval, 34-80). Risk increased significantly with time since treatment for the initial cancer ($P = 0.03$). Detailed treatment data were obtained for 23 cases and 89 matched controls from the childhood cancer cohort. Sixty-eight % of the thyroid cancers arose within the field of radiation. Radiation doses to the thyroid of >200 cGy were associated with a 13-fold increased risk (95% confidence interval, 1.7-104). The risk of thyroid cancer rose with increasing dose ($P < 0.001$), but this was derived almost entirely from the increase from <200 to >200 cCy. The risk of thyroid cancer did not decrease, however, at radiation doses as high as 6000 cGy.

INTRODUCTION

Increased risks of thyroid cancer following exposure to the atomic bombs in Japan (1, 2) and radiation treatment for thymus enlargement (3), tinea capitis (4, 5), and lymphoid hyperplasia (6, 7) are well documented. The actual dose to the thyroid in these studies, however, has been far less than would be delivered by therapeutic radiation for cancer. It is not clear whether the risk of thyroid cancer may decrease after higher dose radiation because the cell-killing effect might outweigh the carcinogenic effect. Although thyroid cancer has been reported after therapeutic radiation for several types of cancer (8–13), few studies have systematically assessed risk following therapeutic levels of external radiation or the effects of chemotherapy on the risk of thyroid cancer.

Factors other than dose have been implicated in the etiology of radiation-induced thyroid cancer. Age at irradiation, time since irradiation, sex, ethnicity, reproductive factors, dietary constituents, and familial predisposition have all been identified as risk factors for thyroid cancer (1–5, 14, 15). We undertook this study to evaluate the risk of thyroid cancer following radiation therapy and chemotherapy used in the management of childhood neoplasms.

PATIENTS AND METHODS

Cohort Analysis. A roster of 9170 patients who survived any type of cancer in childhood for >2 years was constructed from the records of the 13 medical centers participating in the Late Effects Study Group. The period of risk for developing thyroid cancer began 2 years after diagnosis of the primary cancer and ended with the date of death, date of last follow-up, or date of developing a second cancer, whichever occurred first. Person-years of observation were accumulated by means of the computer program of Monson (16). Sex-, age-, and time-specific rates for thyroid cancer incidence obtained from the Connecticut Tumor Registry were applied to the appropriate person-years of observation to estimate the number of cases expected, had this population experienced the same rates prevailing in the Connecticut population (17). Incidence rates from Connecticut were used, since the risk of childhood cancer shows little variation among Western countries (18). Statistical methods for risk estimation were based on the assumption that the observed number of second tumors followed a Poisson distribution. Tests of significance and confidence intervals for the relative risk (observed/expected cases) were calculated by using exact Poisson probabilities. Cumulative probabilities of developing thyroid cancer over time were estimated by the method of Kaplan and Meier (19). To determine the absolute risk, or excess cases of thyroid cancer/10,000 persons/year, the expected number of cases was subtracted from the number observed, the difference was divided by the number of person-years of observation and then multiplied by 10^4. Comparisons between subgroups of relative and excess risks were done using the homogeneity test based on a Poisson distribution (20).

Case-Control Analysis. For each of the 23 thyroid cancer cases, at least two patients without a subsequent neoplasm (a total of 89) were selected as controls by stratified random sampling, matched according to the histology of the first tumor, duration of follow-up (at least as long as the interval between diagnosis of the initial cancer and that of the thyroid cancer), age at the time of diagnosis of the initial tumor (± 2 years), sex, and race. At least one control/case was matched for the calendar year of diagnosis (±2 years) and at least one was not. The diagnoses of the cases and controls were determined from pathology reports. A panel of Late Effects Study Group pathologists confined the histologic findings of all first and second tumors of the cases. For all study subjects, detailed medical and treatment histories were abstracted from the medical records. All data concerning radiotherapy and chemotherapy were collected up to the point of the development of thyroid cancer in each case or the corresponding interval for each matched control. Comparisons between the cases and matched controls were made by the conditional logistic regression method and took into account variable matching ratios (20, 21). The dose of radiation to the thyroid and the amount of chemotherapy were categorized according to the overall distribution of cases and controls, and relative risks were calculated between each category and a referent (lowest dose) category. Tests for trend were performed by designating the midpoint of each dose category as the representative value or score. In addition, we fit linear and linear exponential models to the relative risk to assess dose response using continuous dose data (20). Whenever the matching factors were not correlated with the exposure histories of the cases and controls or the numbers of subjects were so small that the conditions necessary for regression analyses were not present, unmatched analyses were conducted (20, 22).

Radiation Dosimetry. Most of the children were treated with orthovoltage radiation, although higher energy megavoltage units were used during more recent years. Estimated dose to the thyroid gland for each individual was determined for all cases and controls by one of us (M.S.), with adjustment for age at exposure and variables such as height, weight, body surface area, and estimated thyroid gland size as in previous studies (23, 24). The actual conditions of exposure were simulated on the basis of machine characteristics. field configurations,

Received 8/16/90; accepted 3/14/91.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advetrisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] Supported in part by Public Health Service Contract NO1CP-91049 from the Division of Cancer Etiology, National Cancer Institute.

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and treatment conditions and doses to the thyroid of an anthropomorphic phantom were measured similarly to a previous study (25). Collimator head leakage and radiation scatter from the different types of therapy machines were taken into account when possible. For one case and 3 controls who received radiation, no information was available to estimate radiation dose to the thyroid. When the information about radiotherapy was less than adequate (for 3 cases and 16 controls), best estimates of the conditions and exposure were made in consultation with a pediatric radiotherapist (G. J. D'Angio) and considering the hospital, calendar year, tumor site, age, and size of the subject at the time of irradiation.

Chemotherapy Quantification. The total exposures to separate classes of chemotherapeutic agents were measured as previously described, accounting for multiple drug exposures and the amount of drug administered (23, 24). Briefly, for each drug, the total dose received in relation to weight (i.e., mg/kg of body weight) was calculated for each study subject. A distribution of the doses received by all subjects was determined for each drug and then divided into thirds. Each subject was assigned a score of O, 1, 2, or 3 for each drug within a class (e.g., alkylating agents, *Vinca* alkaloids) depending on whether the subject received none of that specific drug or was in the lower, middle, or upper third of each distribution, respectively. The scores of all the drugs within a class were then summed for each subject in order to obtain a score for that drug class. Scores were developed for alkylating agents, *Vinca* alkaloids, other antimetabolites, and dactinomycin.

RESULTS

Cohort Study. Of the 9170 patients surviving for 2 or more years, 55% were male and 45% were younger than 5 years (mean, 7 years; range, O-18 years) when the initial tumor was diagnosed. The mean calendar year of diagnosis was 1969 (range, 1936-1979). The duration of follow-up beginning 2 years after diagnosis of the initial tumor ranged from 2-48 years (mean, 5.5 years) and the entire cohort was followed-up for an aggregate of 50,609 person-years. The distribution of initial tumors was typical of childhood cancers as previously described (26).

Overall, 23 cases of thyroid cancer occurred during the follow-up, compared to 0.4 expected (Table 1) (relative risk, 53; 95% confidence interval, 34-80). The absolute excess risk was 4.6 cases of thyroid cancer/10,000 persons/year. Risks varied nonsignificantly according to sex. A higher RR[3] was seen among males (P = O.12), but a higher excess risk occurred among females (P = O.18). Risks varied by type of initial cancer (P < 0.001), being highest among those treated for neuroblastoma, Wilms' tumor, Hodgkin's disease, and non-Hodgkin's lymphoma. The RR of thyroid cancer was increased among those with early age at initial cancer (P < 0.001), whereas the absolute risk was constant (P = 0.77). The mean age at the time of treatment for the subjects with neuroblastoma was 2 years (range, <1 week-10 years) with a mean radiation dose of 660 cGy (range, 0-3000 cGy). The mean ages for Wilms' tumor, Hodgkin's disease, and non-Hodgkin's lymphoma were 3, 11, and 9 years, respectively, with corresponding mean radiation doses of 310 (range, 0-1500), 3100 (range, 0-7600), and 2400 cGy (range, 0-5600 cGy). Using these mean doses to the thyroid, one can calculate the excess risk/person-year cGy for the cohort data. The risks were 2.1, 1.6, 0.3, and $0.3/10^6$/person-year cGy for neuroblastoma, Wilms' tumor, Hodgkin's disease, and non-Hodgkin's lymphoma, respectively.

The relative and absolute risks increased significantly with time since treatment (P = 0.03: P <0.001. respectively). The cumulative probability (f SE) that thyroid cancer would develop was 4.4 ± 2.0% at 26 years after initial diagnosis for the entire cohort, 6.9 ± 4.0% for males, and 2.O ± 0.6% for females.

Case-Control Study. Of the 23 thyroid cancers, 11 were mixed papillary and follicular adenocarcinoma, 8 were papillary, 3 were follicular, and one was a papillary squamous carcinoma. Of the initial tumors, 7 were neuroblastomas; 5 were Hodgkin's disease; 4 were Wilms' tumor; 2 were non-Hodgkin's lymphoma; and 1 each was teratoma, embryonal sarcoma, ependymoma, medulloblastoma, and malignant histiocytosis.

Sixty-eight % of the thyroid cancers arose within the field of radiation, 27% within 5-10 cm of the field, and 5% >10 cm from the field. All of the cases received at least 100 cGy to the thyroid, while 11 of the controls had no radiation to the thyroid. The radiation dose to the thyroid in all study subjects ranged from 0 to 7600 cGy (mean dose, 1250 cGy median dose, 360 cGy). For the dose-response analyses, the referent category included all cases and controls who received <200 cGy to the thyroid (13% of cases and 49% of controls) (Table 2). The RR associated with >200 cGy was 13.1 (95% CI, 1.7-104). Risk of thyroid cancer was slightly, although nonsignificantly, higher among those receiving >3000 cGy compared to those receiving 200–999 or 1000-2999 cGy. After subdividing the highest dose

Table 1 *Observed and expected cases of secondary thyroid cancer, with relative and absolute excess risks, among children living 2 or more years after diagnosis of a first cancer*

	Patients in cohort	Cases observed	Cases expected	Relative risk[a]	Absolute excess risk[b]
Total	9170	23	0.4	53	4.6
Males	5021	9	0.1	76	3.3
Females	4149	14	0.3	45	5.8
Initial cancer					
Neuroblastoma	790	7	0.02	350	14.0
Hodgkin's disease	1036	5	0.07	67	9.4
Wilms' tumor	1248	4	0.03	132	4.8
Non-Hodgkin's lymphoma	422	2	0.02	81	7.2
Other	5674	5	0.29	17	1.6
Age (yr) at initial cancer					
0–4	4094	11	0.06	169	4.6
5–9	2278	6	0.08	80	5.1
10+	2797	6	0.29	21	3.8
Years since initial cancer					
2–4	9170	1	0.08	13	0.4
5–9	5524	6	0.14	44	3.2
10–14	2288	8	0.12	70	10.2
15–19	979	5	0.07	68	16.6
20+	296	3	0.03	100	33.7

[a] All risks shown statistically significant except for 2–4 years since initial cancer.
[b] Excess cases/10,000 persons/year.

Table 2 *Estimated matched relative risk of thyroid cancer by radiation dose to the thyroid*

	Radiation dose (cGy)			
	<200	200–999	1000–2999	>3000
No. of cases[a]	3	7	7	5
No. of controls	40	17	14	11
Relative risk	1.0[b]	14.2	13.5	17.4
95% confidence interval		1.7–122	1.4–127	1.4–217
Relative risk[c]	1.0[b]	13.1	12.1	17.6
95% confidence interval		1.5–114	1.3–117	1.4–226

[a] Study subjects with unknown radiation dose to the thyroid (one case, 7 controls) are not included.
[b] Referent category.
[c] Adjusted for dactinomycin USC.

[3] The abbreviations used are: RR, relative risk: Cl, confidence interval

category to 3000-5999 and >=6000 cGy, the risk did not decrease in the study subjects treated with >6000 cGy to the thyroid (RR 16.5 and 21, respectively). There was a significant trend in risk with increasing dose ($P < 0.001$), but this was derived almost entirely from the increase from <200 to >200 cGy. There was no significant difference in fitting linear exponential and linear cell-killing models in the excess relative risk ($x^2 = 2.9$; $P = 0.09$). Any apparent curvilinearity was due to doses <200 cGy.

The patterns of dose to the thyroid varied by age. Among the cases treated before age 5 years, all received <3000 cGy to the thyroid, and 82% received <1000 cGy. In contrast, only one of the cases older than 5 years when treated received Cl 000 cGy, and 50% received >3000 cGy. It was therefore not possible to compare equivalent radiation doses directly in the different age groups. It was also impossible to disentangle the effects of the latency between the initial cancer and thyroid cancer, age at time of treatment, and radiation dose. Forty-six % (5 of 11) of those treated before age 5 years, 33% (2 of 6) of those treated at ages 5-9 years, and 17% (1 of 6) of those treated after age 10 years developed thyroid cancer >15 years after treatment.

The risk of thyroid cancer associated with chemotherapy was also assessed. There was no significant excess risk following exposure to alkylating agents, controlled for radiation (RR 1.2; 95% CI 0.4-3.8). There was also no indication of increasing risk with higher doses of alkylating agents (RR 1.0). No excess risk was associated with *Vinca* alkaloid treatment (RR 1.0) even in the higher dose categories (RR 0.5). After dactinomycin treatment, there was a small and statistically nonsignificant increase in risk on the basis of small numbers, adjusted for radiation (RR 1.7, 95% CI 0.3-11.6) but no indication of dose response. There was no evidence of increased risk associated with chemotherapy among subjects who received <200 cGy to the thyroid and dactinomycin (Table 3) but a suggestion of increased risk in those who received higher dose radiation and dactinomycin, compared to those treated with radiation and no dactinomycin. The mean latency between treatment with dactinomycin and development of thyroid cancer was 13.8 years (range, 6.7-20.6 years).

There were no case-control differences in the family history of thyroid or other cancers reported at the time of the diagnosis of the initial cancer. In addition, no case-control differences were noted in ethnicity or religion.

Table 3 *Estimated matched relative risk of thyroid cancer by radiation dose and dactinomycin use*

	Dactinomycin	
Radiation dose	No	Yes
<200 cGy		
Cases:controls[a]	3:28	0:12
Relative risk	1.0[b]	0
200–999 cGy		
Cases:controls	4:12	3:5
Relative risk	10	4.3
95% CI	0.8–121	0.2–94
≥1000 cGy		
Cases:controls	9:24	3:1
Relative risk	9.2	39
95% CI	0.9–97	1.6–947

[a] Study subjects with unknown radiation dose to the thyroid (one case, 7 controls) are not included.
[b] Referent category.

DISCUSSION

This multicenter study revealed a 53-fold increased risk of thyroid cancer after childhood cancer, mainly due to the use of radiation therapy. The risks were elevated at all dose levels, even >6000 cGy. Although a decrease in risk at the highest doses was not observed, the risk was lower than what would have been predicted based on children exposed to much lower doses (3, 5), suggesting the possible influence of some cell-killing effects. It is noteworthy that in the case-control study, the referent group consisted of study subjects who received up to 200 cGy to their thyroid. Other studies have found approximately 10-fold increases in risk of thyroid cancer with radiation doses between 1 and 200 cGy (12).

Most other studies of radiogenic thyroid cancer have evaluated risks associated with much lower doses. Shore *et al.* (3) found a linear dose-response curve for thyroid cancer following thymus irradiation, with doses ranging from 5 to 1000 cGy (62% received <50 cGy). Ron *et al.* (5) observed a 4-fold increased risk of thyroid cancer after 9 cGy to the thyroid from scalp irradiation for tinea capitis. Based on clinical examination data, Pottern et *al.* (7) reported a 2.7-fold increased risk of thyroid nodules (the risk for thyroid cancer was not quantified) at 24 cGy from irradiation for hypertrophied tonsils (7). Based on these risk estimates from much lower dose data (3-5, 7), RR on the order of 200-900 would have been predicted among those receiving 3000 cGy compared to nonirradiated children. The referent group in this study, however, may have had a 10-fold risk compared to nonirradiated children. Thus, if a 10-fold risk is assumed in the referent category, the risk in this study for those receiving 3000 cGy is closer to 180. The large increase in risk from <200 to >200 cGy and the relatively flat dose-response curve at the higher doses imply a diminution of incremental increases in risk at these dose levels.

The risk of thyroid cancer increased significantly with elapsed time since initial treatment, up through 20 years, consistent with the temporal distribution of risk reported for various radiation-induced tumors (1, 13, 24). This finding has important implications for the clinical follow-up of these patients, since they continue to be at excess risk of thyroid cancer at least 20 years after initial treatment.

It has been proposed that age at radiation exposure is an important factor in the development of thyroid cancer (1, 3-5, 7). Individuals treated at an early age appeared to have a higher relative risk of thyroid cancer in the cohort study, but the estimates of the expected numbers are very small and unstable. The excess numbers of thyroid cancers did not vary appreciably by age. The data from the case-control study also revealed that the individuals treated at an earlier age developed thyroid cancer after lower doses of radiation, which might suggest some increased sensitivity to radiation. We were unable to separate the effects of age at the time of treatment and dose in the case-control study, since equivalent doses were not given to the different age groups.

The different levels of risk associated with type of first cancer in the cohort study may reflect the age at treatment and radiation dose. The higher excess risks of thyroid cancer among the children with neuroblastoma and Wilms' tumor treated at younger ages with lower doses are consistent with an age-at-treatment effect. An alternative explanation of these data could be a cell-killing effect at higher doses, which may reduce, but does not eliminate, the risk.

For Hodgkin's disease. there are equivalent data for individ-

uals treated as adults (27). In contrast to a 67-fold increased risk of thyroid cancer among children treated at a mean age of 12 years, the risk of thyroid cancer after 15 years in 1507 individuals treated at a mean age of 29 years with similar therapeutic regimens showed only a modest, nonsignificant increase. In the Connecticut tumor registry, there was a 7-fold increased risk of thyroid cancer among 3211 individuals treated at an average age of 40 years for Hodgkin's disease (28). Sixty-six % of these individuals received some radiation as initial treatment for Hodgkin's disease. These data, although limited, lend credence to the age-at-treatment hypothesis, since the initial disease and treatments did not vary, but the age at the time of treatment did.

The chemotherapy data appear too limited to support strong conclusions, but we found no effect of alkylating agents on the risk of thyroid cancer. This is interesting in light of the similar mechanisms of action of alkylating agents and radiation and our finding that alkylating agents affect the risk of bone sarcomas, another radiation-induced cancer (24). On the basis of small numbers, there was no evidence from this study that dactinomycin is protective against radiation-induced cancers as previously described (29). This may be due to the difference in the comparison groups in the studies.

Although no case-control differences were found in the family history of thyroid or other cancers, the comparisons were based on data available in the medical records from the time of diagnosis of the initial cancer. No information was available for both the cases and controls at the time of diagnosis of thyroid cancer, when siblings are more likely to attain the age at risk of thyroid cancer.

The results of this study should be viewed in light of some methodologic concerns. Although the individual radiation dose to the thyroid was calculated for 83% of the study subjects, for 17%, some information about treatment was not available and best estimates were made. Excluding the study subjects with estimated doses increased the risks associated with each level of radiation dose. Using only the controls that were matched on calendar year increased the relative risks associated with radiation dose, compared to using only the controls not matched on calendar year. The controls not matched on calendar year received higher doses of radiation to the thyroid (mean, 1200 cGy, median, 265 cGy; range, 0-6400 cGy) than the controls matched on calendar year (mean, 900 cGy, median, 155 cGy range, 0-4700 cGy). The median year of diagnosis was 1962 for the calendar year-matched controls and 1959 for the others.

The radiogenic risks of thyroid cancer in this study must be put in perspective. During the time interval in which these patients were treated, significant therapeutic advances were made which have resulted in thousands of children surviving extended periods of time. The small cumulative risk of thyroid cancer (approximately 4% at 26 years) should not discourage the use of radiotherapy or other established forms of cancer treatment. particularly since thyroid cancer can be easily diagnosed and treated. The temporal increases in risk underscore the importance of long-term surveillance of individuals whose thyroids were irradiated in childhood.

ACKNOWLEDGMENTS

We are indebted to the many physicians and other personnel at the Late Effects Study Group member institutions without whom this study would have been impossible and to Dr. Giulio D'Angio for consultation.

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